

REMARKS

Applicants note with appreciation the Examiner's indication that any rejections from previous office actions that have not been reiterated in the present Office Action have been obviated (Office Action at 2). Applicants assume, then, that the previous rejections under 35 U.S.C. § 102 may be considered withdrawn.

Discussion of the Amendment

Claim 1 has been cancelled, and rewritten in its entirety as new claim 13, as discussed in detail below.

Claim 3 has been cancelled to remove it from a multiple dependent format. Claim 3, as dependent on claim 1 has been rewritten in independent format as new claim 14. Claim 3, as dependent on claim 2 has been rewritten as new claim 15.

Claims 3, 4 and 7, with previous dependencies on cancelled claim 1, have been amended to depend on new claim 13.

Claim 16 has been added, as dependent upon claim 4, to claim the first two named compounds of claim 4.

This amendment to the claims adds no new matter.

As presently amended, claims 2, 4, 7, 13, 14, 15 and 16 are pending in this application.

Discussion of the Rejection Under 35 U.S.C. § 112

The Examiner has rejected cancelled claim 1 under 35 U.S.C. § 112, second paragraph as, the Examiner alleges, “being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” (Office Action at 4).

The Examiner goes on to assert,

It is unclear as to what is the recitation of  $[-\text{NO}_2]$  is meant to represent. The use of brackets is generally understood to mean that the information provided within the brackets has been newly added but the recitation of R5 consisting of  $-\text{NO}_2$  was already present in the claims prior to the amendment filed 1/18/07. (Office Action at 4).

Notwithstanding the Examiner’s assertion, this is not the case. 37 C.F.R. § 1.121(c)(2) provides,

The text of any deleted subject matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. (Emphasis Added)

In the case of the amendment to claim 1 filed by Applicant on January 17, 2007, deletion of “halogen” was indicated by strike-through, and deletion of  $-\text{NO}_2$  was indicated by double brackets before and after. This was permitted because  $-\text{NO}_2$  contained less than five characters. Applicants also believed deletion by double brackets was required because strike-through of the bond portion (-) of  $-\text{NO}_2$  was believed to be difficult to perceive.

However, as a courtesy to the Examiner, claim 1 has been cancelled, and rewritten, in its entirety as previously amended, as new claim 13.

In rewriting claim 1 as new claim 13, inadvertent errors whereby “or” was included after  $-\text{CF}_3$ , and whereby “or” was recited instead of “and” after “2-furyl” have been corrected.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 are respectfully requested.

Discussion of the Rejections Under 35 U.S.C. § 103

In the following discussions, for consistency with Applicants' previous response, U.S. 5,792,783 will be referred to as "Tang 1", U.S. 6,316,429 will be referred to as "Tang 2", and U.S. 6,133,305 will be referred to as "Tang 3".

The Examiner has rejected claims 1 to 4 and 7 (as previously presented, now claims 13, 2, 4, 7, 14 and 15) under 35 U.S.C. §103(a) as, the Examiner asserts, being unpatentable over Tang 1 (Office Action at 4).

It is well-settled that a species or sub-genus is not necessarily rendered obvious by a prior disclosed genus. (See, for example, *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); and MPEP 2144.08). Among the factors to be considered are the size of the disclosed genus, the express teachings of the reference disclosing the genus, the teachings of structural similarities, the teaching of similar properties or uses, and the predictability of the technology (MPEP 2144.08).

The number of compounds disclosed by each of the genera of Tang 1 is enormous. However, nowhere in Tang 1 are the compounds as defined by the claims of the present invention specifically disclosed. Further, no guidance is found in Tang 1 to lead a person skilled in the art to specifically pursue the compounds of the present application. This is true for all compounds of the present invention.

To arrive at compounds of the present invention, one must make the multiple selection (as acknowledged by the Examiner in the Office Action at 4), that R<sub>1</sub> of Tang 1 is H, R<sub>2</sub> is oxygen, R<sub>3</sub> is hydrogen, R<sub>4</sub>, R<sub>6</sub> and R<sub>7</sub> are hydrogen, R<sub>5</sub> is aryl (in particular 3-pyridyl and 5-pyrimidinyl as required by the present invention for an aryl group at the R<sub>5</sub> position) or R<sub>5</sub> is

alkanoylamino. To these selections would be added  $-\text{CONH-(C}_1\text{-C}_4\text{ alkyl)}$ ,  $\text{SO}_2\text{NH}_2$ ,  $-\text{CF}_3$ , and  $\text{CO}_2\text{R}$ , which are also claimed at the R5 position of the compounds of the present invention. Finally, A of Tang 1 (Analogous to Ar of the present invention) would have to be selected as 2-pyrrolyl, 5-imidazolyl, 2-thiazolyl or 2-furyl.

There is simply no guidance in Tang 1 to make the specific selection of the eight variable moieties to arrive at the compounds of the present invention.

This is true, in particular, for the compound of Applicants' elected species, 1,3-dihydro-3-(imidazol-4-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one, and for the compound 1,3-dihydro-3-(pyrrol-2-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one. None of the compounds exemplified or specifically disclosed by Tang 1 contain an imidazolylmethylene moiety at the 3-position (or any other position for that matter) of the indolinone ring. Further, the only moieties specifically disclosed by Tang 1 at the 5-position are chloro, nitro and methoxy. None of the compounds exemplified or specifically disclosed by Tang 1 contain any aromatic moiety at the 5-position, let alone the pyridyl moiety as required by these compounds.

Further, there is no disclosure in Tang 1, nor any suggestion of using the compounds disclosed therein as inhibitors of CDK-1.

Because the genera of Tang 1 encompass an enormous number of compounds; because there is no specific disclosure of any of the compounds of the present invention; because there is no guidance in Tang 1 as to the desirability of the particular moieties and placement thereof on the indolinone ring as required by the compounds of the present invention; and because the compounds of the present invention have a utility undisclosed by Tang 1, Tang 1 does not render the present invention obvious over 35 U.S.C. § 103(a).

The Examiner has rejected claims 1 to 4 and 7 (as previously presented, now claims 13, 2, 4, 7, 14 and 15) under 35 U.S.C. §103(a) as, the Examiner asserts, being unpatentable over Tang 2 (Office Action at 5).

The discussion above applies also to Tang 2. The generic disclosure of Tang 2 is absolutely enormous. Meanwhile, Table 1 of Tang 2 lists 133 starting indolinones, and 112 starting aldehydes, giving rise to almost 15,000 compounds which may be thought of as specifically disclosed. In spite of this, there is no specific disclosure of any of the compounds as defined by the claims of the present invention.

Applicants acknowledge that pyrroles, thiophenes, and furans are listed in Table 2 of Tang 2 and, as such, form substituents analogous to the “Ar” portion of Applicants’ Formula 1. However, these aromatic substituents are invariably substituted with one or more carboxyalkyl substituents, or esters or amides thereof. These substituents could certainly have an effect on the properties of the molecules. These substituents are simply not present in any of the compounds of the present application, and there is no specific indication in Tang 2 that compounds so unsubstituted would be useful as kinase inhibitors of any kind, let alone as inhibitors of CDK-1.

Further, with regard to Applicants’ elected species, 1,3-dihydro-3-(imidazol-4-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one, and for the compound 1,3-dihydro-3-(pyrrol-2-ylmethylene)-5-pyrid-3-yl)-2H-indolin-2-one, there is no specific disclosure of any imidazole at the 3-position of the indolinone ring, as required by Applicants’ elected species, and there is no disclosure of any directly attached aromatic ring at the 5-position, let alone any disclosure of pyridyl.

Accordingly, because the genera of Tang 1 encompass an enormous number of compounds; because there is no specific disclosure of any of the compounds of the present invention; because there is no guidance in Tang 1 as to the desirability of the particular moieties and placement thereof on the indolinone ring as required by the compounds of the present invention; and because the compounds of the present invention have a utility undisclosed by Tang 2 (i.e., inhibition of CDK-1), Tang 2 does not render the present invention obvious over 35 U.S.C. § 103(a).

The Examiner has rejected claims 1 to 4 and 7 (now claims 13, 2, 4, 7, 14 and 15) under 35 U.S.C. §103(a) as, the Examiner asserts, being unpatentable over Tang 3, in view of Tang 1. (Office Action at 2).

The Examiner states that, “Applicant is incorrect in the assertion that [Tang 1] does not provide for an imidazolylmethylene at the 3-position.” (Office Action at 3). Applicants’ have not asserted that Tang 1 does not provide for an imidazolylmethylene at the 3-position. However, although generically disclosed as a possible value for “A” of Tang 1, there is no specific disclosure of this moiety in Tang 1.

Further, the Examiner has acknowledged the novelty of the compounds of the present invention, indicating that there is no specific disclosure of the present compounds in the prior art.

As pointed out above, it is well-settled that a species or sub-genus is not necessarily rendered obvious by a prior disclosed genus.

The generic disclosure of Tang 3 is massive. Further, looking at Tables 1 and 2 of Tang 3, combining the indolinones and aldehydes of Tables 1 and 2, respectively, gives rise to almost 2,000 compounds that can be thought of as specifically disclosed. None of the compounds encompassed by the claims of the present application are specifically disclosed. In particular, and as the Examiner acknowledges, the compounds of Tang 3 do not contain the substituents of the instant claims at the 5-position (Office Action at 3).

Applicants acknowledge that Tang 3 discloses an indolinone substituted at the 3-position by a pyrrol-2-ylmethylidienyl or imidazol-4-ylmethylidienyl (see examples 10717/H04, 10717/H09, 10724/H09 and 10725/H11 in Table 3 of Tang 3). However, these examples are invariably substituted with halogen atoms at positions 5 and 7 of the indolinone ring. Nothing in Tang 3 would suggest to, or motivate a person skilled in the art to key on or pursue these particular examples out of the hundreds of others. There would be even less motivation to combine these four examples with the disclosure of Tang 1 to arrive at the compounds of the present invention, absent the disclosure of the present application.

The Examiner appears to be using the disclosure of the present application and hindsight to suggest motivation to combine Tang 1 and Tang 3. Such use of hindsight in an obviousness analysis is impermissible. (See, for example, *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), and MPEP 2143.01).

It is well settled that obviousness to try, without a reasonable expectation of success is not the proper standard under 35 U.S.C. § 103. (See, for example, MPEP 2143.02; *In re Eli Lilly & Co.*, 14 U.S.P.Z.2d 1741, 1743 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988)). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” (*In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988)).

The compounds of the present application are inhibitors of the Cdc2/cyclin B (CDK-1) enzymatic complex, which is responsible for initiating phase M of the cell cycle. Modulation of the activity of CDK-1 is a key mechanism for halting cell proliferation. (See, for example, the present specification at page 2).

Tang 1 relates to compounds that modulate or inhibit tyrosine kinase signal transduction. Tang 1 does not describe the use of the compounds disclosed therein as specific inhibitors of CDK-1, in particular in order to stop cell proliferation at phase G2/M. Similarly, Tang 3 does not specifically disclose the use of the compounds disclosed therein to inhibit CDK-1.

Thus, even if combining Tang 1 and Tang 3 were to somehow render it obvious to try compounds of the present invention as CDK-1 inhibitor (which, as discussed above, it does not) there could certainly be no expectation of success derived from the disclosures of Tang 1 and Tang 3.

Accordingly, in view of the present amendment and above remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

In view of the present amendment and the above remarks, Applicants submit that the invention as defined by the claims of the present application is novel and non-obvious over the prior art, and complies with the provisions of 35 U.S.C. § 112. Therefore, allowance and passage to issue of Claims 2, 4, 7, 13, 14, 15 and 16 are respectfully requested.

The Commissioner is hereby authorized to charge any additional fees that may be required for this filing, or credit any overpayment to Deposit Account Number 18-1982, upon which the undersigned is authorized to draw.

Respectfully submitted,

  
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